

Jay Berzofsky, et al.
Application No. 09/508,552
Page 5

PATENT

- II. Claims 1-15, 17, 25-36, 38, 46-65, and 67-69, drawn to influenza antigens classified in Class 424, subclass 85.6,
- III. Claims 1-15, 18, 25-36, 39, 46-65, and 67-69, drawn to rotavirus antigens, classified in Class 424, subclass 85.6, and
- IV. Claims 1-14, 19, 25-35, 46-65, and 67-69, drawn to (bacterial and protozoan antigens), classified in Class 424, subclass 85.6.

Applicants elect to prosecute Group I, claims 1-16, 21-37, and 42-69, wherein the claims are drawn to compositions and methods using HIV-1 antigens, with traverse. Applicants reserve the right to file a divisional or related application to the claims of the non-elected groups. Further, the Examiner has requested election of a single disclosed species from the specific individual HIV-1 peptides in claims 21-24, 42-45, and 66 for continued prosecution. The Examiner has indicated claims 1-16, 25-37, 46-65, and 67-69 as generic. Applicants elect HIV-1 cluster peptide PCLUS3-18IIB (SEQ ID NO: 2), as the species for substantive examination with traverse. Further, Applicants note that upon an indication of allowability of a generic claim, a reasonable number of additional species will be considered and can also be claimed in the same application as provided by 37 CFR § 141.

Prior to remarks relating to the traverse of the restriction requirement, Applicants note that the description of the claims of Group IV (claims 1-14, 19, 25-35, 46-65, and 67-69) is incomplete. It appears that the phrase should have read "drawn to bacterial and protozoan antigens" to describe the claims of the group. Further, it is respectfully noted that claim 20 was not included in any claim group and it appears that the Examiner may have intended another separate group.

It is respectfully requested that the Examiner reconsider this request for restriction in order that Applicants might be allowed a compact and expedited prosecution of the present invention and to provide a patent which adequately protects the entire invention.

Restriction can be required by the Office for certain reasons as set forth in the MPEP under section 800. Such restriction is entirely at the discretion of the Office. Restriction is required so that an undue burden is not placed on the Office in prosecuting the application, so that the statutory fee structure is not subverted, and so that the integrity of the

Jay Berzofsky, et al.
Application No. 09/508,552
Page 6

PATENT

examination and classification system of the Office are not jeopardized. Requirement for restriction is balanced against the right of the Applicants to claim their invention as they require to adequately protect their invention and to provide for a compact and expedited prosecution.

Applicants respectfully submit that the presently claimed invention relates to methods which together comprise a single inventive concept. Under 35 U.S.C. § 121, there are two criteria for a proper requirement for restriction between patentably distinct inventions:

- (1) the inventions must be independent or distinct as claimed; and
- (2) there must be a serious burden on the examiner if restriction is not

required.

See MPEP § 803.

Applicants submit that these criteria are not met by the presently claimed invention which relates to the single inventive concept of methods of inducing a protective mucosal cytotoxic T lymphocyte response in a mammalian subject comprising contacting a mucosal tissue of the subject with a composition comprising a purified soluble antigen. Specifically, the present invention provides a method for inducing a protective mucosal cytotoxic T lymphocyte response using any one or more of a number of distinct soluble peptides from a number of sources including, for example, pathogenic viruses (including HIV-1, influenza, and rotavirus) as well as peptides from a pathogenic bacteria or protozoan, or a tumor-associated peptide. The methods, as claimed, can also comprise administering a composition further comprising a cytokine with or without interferon γ . Because these method claims represent a single inventive concept, Applicants believe they properly encompass a single prosecutable invention.

Second, Applicants believe that because the present claims comprise a single inventive concept, any search of the patent or scientific literature directed to methods for inducing a protective mucosal cytotoxic T lymphocyte response would be expected to encompass art in the field of the invention as claimed. It should be further noted that each of the Groups as set forth by the Examiner are classified in the same class and even subclass. Thus, prosecution of the invention, as a whole, should not place a burden on the Examiner

Jay Berzofsky, et al.
Application No. 09/508,552
Page 7

PATENT

sufficient to justify restriction. Therefore, Applicants respectfully request that the Examiner reconsider this request for restriction.

Further, the Examiner noted certain typographical and clerical errors in the claims and has requested correction. Specifically, the Examiner noted that claim 5 lacked basis for "cytokine"; claim 48 had a typographical error in "absorption"; and claim 66 depended from itself.

Applicants have reviewed the claims and the specification for the errors noted by the Examiner and others. Specifically, Applicants note that claim 5 properly recites "cytokine", but that claim 6 has been amended to be dependent from claim 5 and not claim 1 to correct antecedent basis for "cytokine." Further, at page 5, line 4, the spelling of absorption has been corrected. At page 6, line 27 and page 24, line 11, the spelling of cyclodextrin has been corrected. Also, at page 9, line 5, the designation of 160IIIIB. has been corrected. Further, at page 11, line 18, the designation for CD8⁺ cells has been corrected and at page 39, line 24 "(50© µg /mouse)" has been corrected to "(50 µg/mouse)". Finally, at page 48, line 6, "note" has been replaced with "not".

All of the amendments to the specification are to correct various typographical and clerical errors. No new matters is believed to have been added by any amendment to the claims or to the specification discussed above.

Jay Berzofsky, et al.
Application No. 09/508,552
Page 8

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If for any reason the Examiner believes that a telephone conference would expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 5 December 2001

By: Brian W. Poor
Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, CA 94111
(206) 467-9600
SE 5010833 v1

Jay Berzofsky, et al.
Application No. 09/508,552
Page 9

PATENT

APPENDIX

Version With Markings to Show Changes Made

IN THE SPECIFICATION:

Kindly replace the paragraph at page 5, line 34 to page 6, line 4, with the following paragraph:

Also provided within the invention are immunogenic compositions for inducing a protective mucosal CTL response in a subject which are adapted for intrarectal administration. The compositions comprise a purified soluble antigen formulated for intrarectal delivery to the rectum, colon, sigmoid colon, or distal colon. They may be formulated as a rectal enema, foam, suppository, or topical gel and generally comprise a base, carrier, or [absorption-promoting] absorption-promoting agent adapted for intrarectal delivery.

Kindly replace the paragraph at page 6, lines 23-28, with the following paragraph:

To optimize intrarectal delivery, the immunogenic compositions of the invention also preferably include an absorption-promoting agent, for example a surfactant, mixed micelle, enamine, nitric oxide donor, sodium salicylate, glycerol ester of acetoacetic acid, [cyclodextrin] cyclodextrin or beta-cyclodextrin derivative, or medium-chain fatty acid.

Kindly replace the paragraph at page 9, lines 1-8, with the following paragraph:

Fig. 11 demonstrates that protection induced by mucosal immunization with HIV-1 peptide vaccine is specific. On day 35, mice were challenged intrarectally with 2.5×10^7 plaque-forming units (pfu) of vaccinia virus expressing gp [160IIIB] 160IIIB (vPE16) or with 2.5×10^7 pfu of vaccinia virus expressing β -galactosidase (vSC8). Bars = SEM of five mice per group. The difference is significant at $P < 0.01$ by Student's test.

Jay Berzofsky, et al.
Application No. 09/508,552
Page 10

PATENT

Kindly replace the paragraph at page 11, lines 10-35, with the following paragraph:

IR immunization induced long-lasting protective immune responses. For example, antigen-specific CTL were found in both mucosal and systemic sites 6 months after immunization. IR immunization with the antigenic peptide elicited significantly stronger CTL responses than IN immunization with the same peptide. While IR administration with PCLUS3-18IIB (SEQ ID NO:2) induced a significant response when administered alone, the response was enhanced by the inclusion of CT. The CTL were [CDB+] CD8⁺ T lymphocytes restricted by MHC class I molecules, recognizing MHC class I positive target cells either endogenously expressing *HIV-1* gp160 or pulsed with an appropriate gp160 peptide. Induction of both mucosal and systemic CTL response by IR immunization was IL-12-dependent, as shown by inhibition of induction of CTL in mice treated i.p. with anti-IL-12 antibody. Furthermore, inclusion of IL-12 in the composition of antigenic peptide and CT used for IR immunization resulted in enhanced mucosal and systemic CTL responses relative to the responses elicited by antigenic peptide and CT without IL-12. The dependence on IFN γ of mucosal and systemic CTL generation following IR immunization was demonstrated by the absence of such responses in mice which lack the ability to produce functional IFN γ , e.g., as the result of a premature stop-codon in the IFN γ -encoding gene. The stop-codon mutation causes the gene to encode a truncated protein lacking the activity of IFN γ .

Kindly replace the paragraph at page 24, lines 7-21, with the following paragraph:

Accordingly, preferred formulations for administering soluble antigens and CTL-stimulatory cytokines within the methods of the invention are designed to optimize mucosal delivery. These agents may thus include [cycloextrins] cyclodextrins and beta-cyclodextrin derivatives (eg., 2-hydroxypropyl-beta-cyclodextrin and heptakis(2,6-di-O-methyl-beta-cyclodextrin). These compounds, preferably conjugated with one or more of the active ingredients and formulated in an oleaginous base, are well documented to enhance

Jay Berzofsky, et al.
Application No. 09/508,552
Page 11

PATENT

bioavailability in intrarectal formulations. Other absorption-enhancing agents adapted for intrarectal delivery include medium-chain fatty acids, including mono- and diglycerides (eg., sodium caprate--extracts of coconut oil, Capmul), and triglycerides (eg., amyloextrin, Estaram 299, Miglyol 810).

Kindly replace the paragraph at page 39, lines 21-32, with the following paragraph:

Immunization Mice were immunized with 4 doses of the synthetic HIV peptide vaccine construct PCLUS3-18IIIB (Ahlers et al., J. Immunol. 150:5647-5665, (1993)) ([50 μ g/mouse] for each immunization) (50 μ g/mouse for each immunization) on days 0, 7, 14 and 21 in combination with cholera toxin (CT) (10 μ g/mouse) (List Biological Laboratories, Campbell, CA) by intrarectal administration. For subcutaneous immunization, incomplete Freund's adjuvant was used. rm IL-12 (a generous gift of Genetics Institute, Inc., Cambridge, MA) was delivered either intraperitoneally (IP) (1 μ g) or intrarectally (1 μ g) mixed with DOTAP (Boehringer Mannheim), a cationic lipofection agent, along with the peptide vaccine.

Kindly replace the paragraph at page 48, lines 3-7, with the following paragraph:

One possible difference between CTL induced by mucosal versus systemic immunization is that the CTL resulting from the SC immunization do not have homing receptors for the GI mucosa, as evidenced by the fact that they are [note] not detected in the lamina propria or Peyer's patches.

IN THE CLAIMS:

Kindly replace claims 6, 27, 48 and 66 with the following substitute claims. An Appendix showing all changes to these claims is attached to this amendment as required by 37 CFR §1.121(c).

Jay Berzofsky, et al.
Application No. 09/508,552
Page 12

PATENT

1 6. (Amended) The method of claim [1] 5, wherein the cytokine is contacted
2 with a mucosal surface of the subject.

1 27. (Amended) The method of claim [25] 26, wherein the cytokine is contacted
2 with a mucosal surface of the subject.

1 48. (Amended) The immunogenic composition of claim 46, further comprising
2 a base, carrier, or [aabsorption-promoting] absorption-promoting agent adapted for intrarectal
3 delivery.

1 66. (Amended) The immunogenic composition of claim [66] 64, wherein the
2 protein or peptide is an HIV V3 loop or T cell-binding peptide fragment thereof.